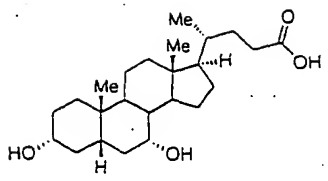
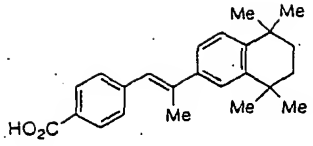
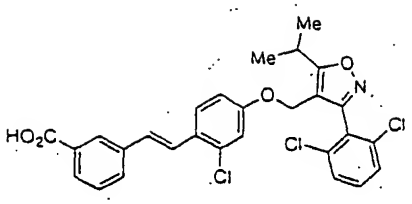


1: CDCA (low affinity endogenous agonist)



2: TTNPB (low affinity agonist; EC_{50} > 1μM)

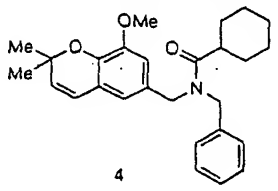


3: GW 4064 (high affinity agonist; EC_{50} = 80 nM)[a]

Figure 1. Natural and synthetic agonists of FXR (farnesoid X receptor). [a] Cell based assay.

FIG. 1

a. Initial high throughput leads.



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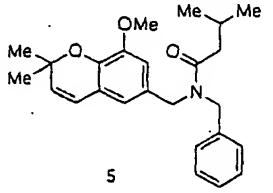

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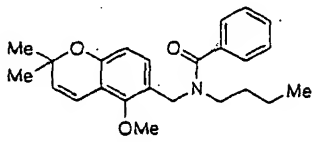

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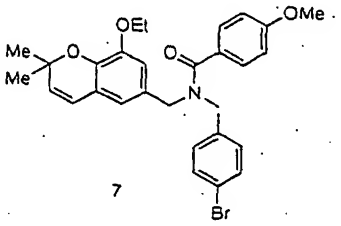

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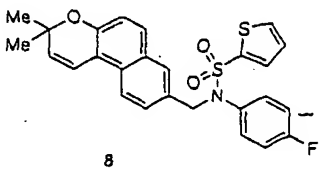

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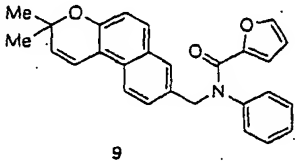

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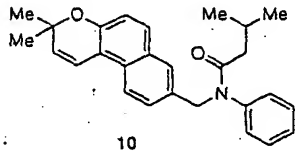

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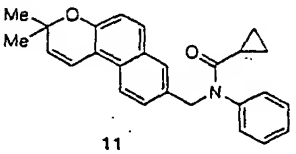

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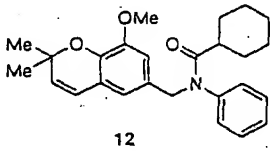

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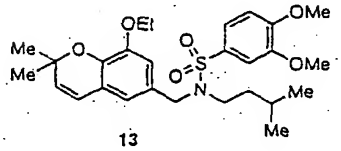

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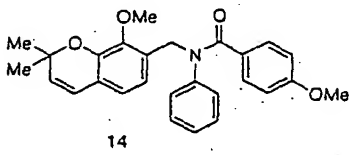

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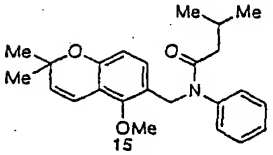
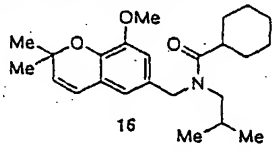


15

b. Focused library leads.



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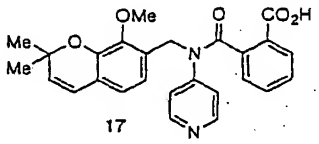

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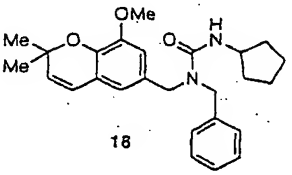

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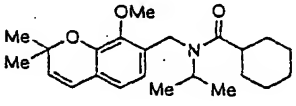

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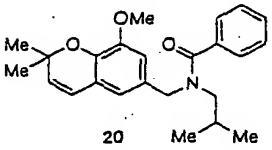

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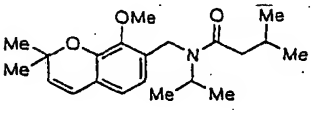

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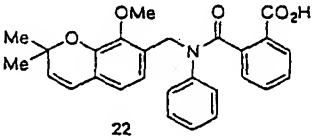

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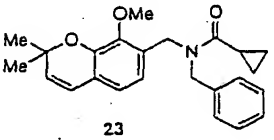

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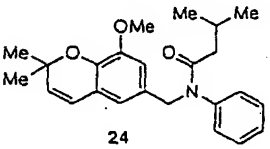

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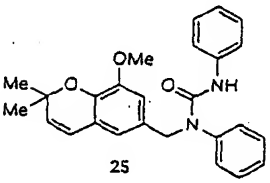

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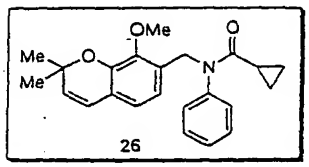

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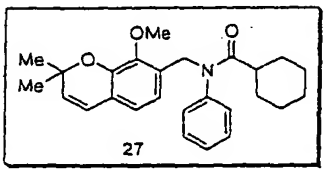
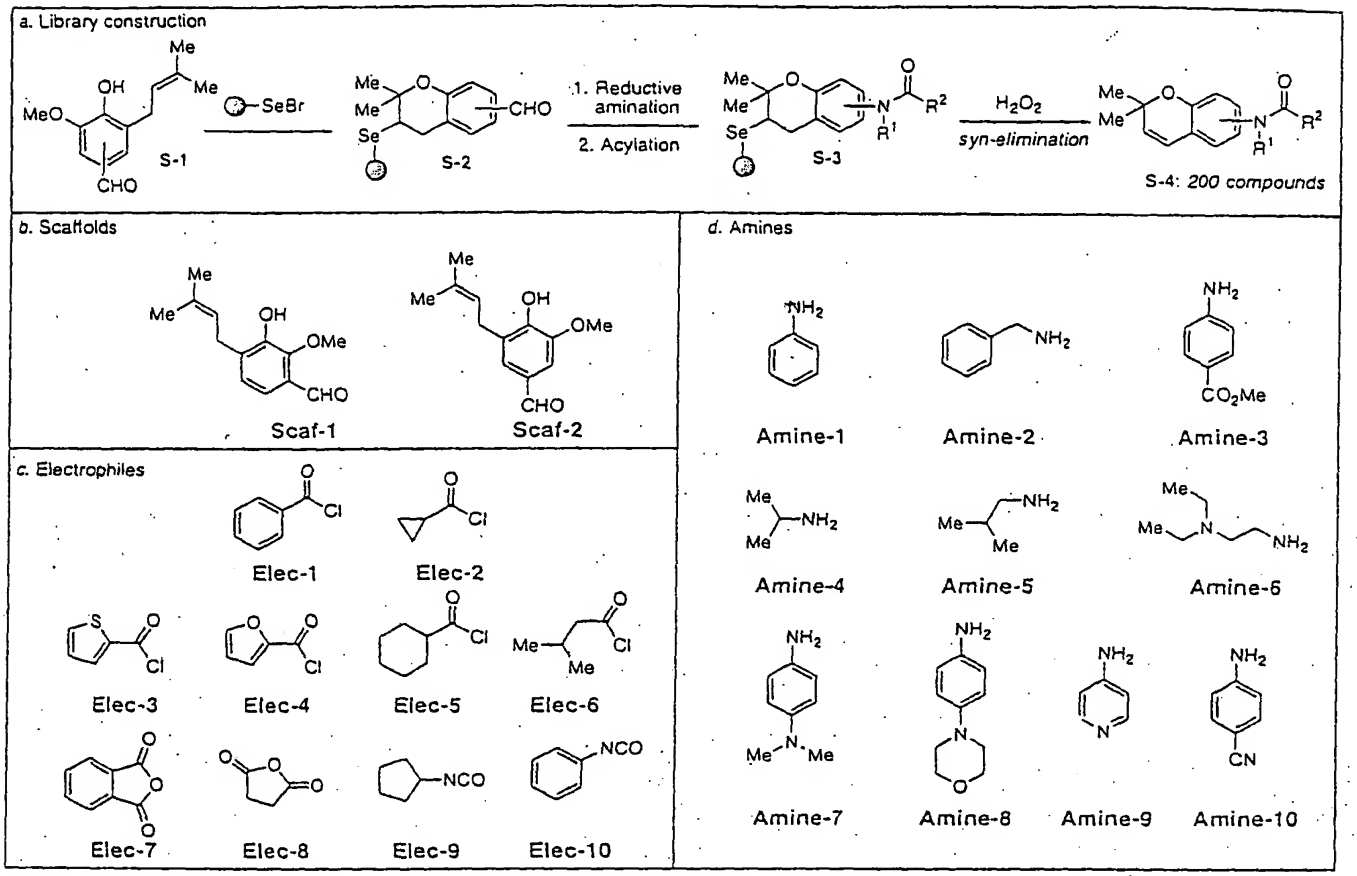


27

Selected hits from a high throughput screen for FXR agonism of a 10,000-membered benzopyran-based natural product-like library (EC_{50} = 5-10 μM). b) Selected low affinity FXR agonists from follow-up solid phase benzopyran library (EC_{50} = 5-10 μM). See Figure 3 for details of the focused library synthesis. The boxed compounds represent the most potent FXR agonists.

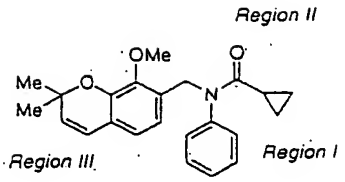
FIG. 2A
2B

Solid-phase synthesis of a focused library of benzopyran containing small molecules as potential FXR agonists.[a]



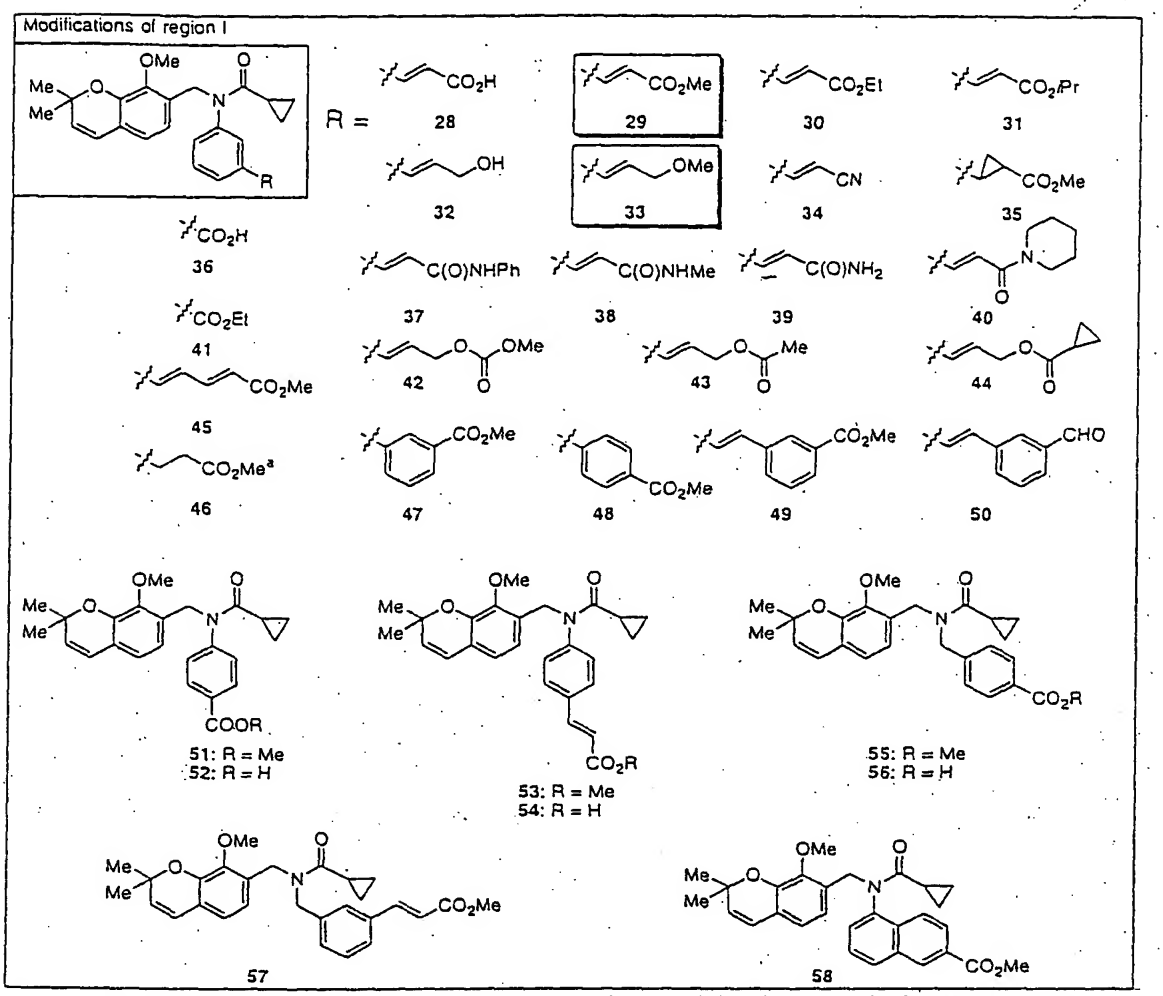
[a]Panel a) solid-phase protocol. Panel b) o-prenylated phenols employed as scaffolds. Panel c) Electrophiles employed. Panel d) Amines employed. Reagents and conditions: See reference 21.

FIG. 3



Selected regions of interest for SAR evaluation of lead compound 26. Region I: Right-hand aromatic system; Region II: Acyl group region; Region III: Left-hand benzopyran ring system.

FIG. 4

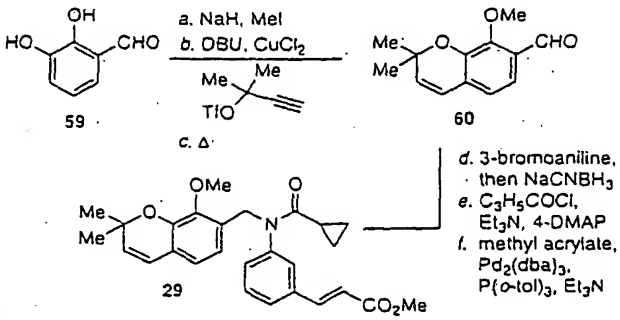


. Examination of Region I SAR. See Figures 6, 7, 9 and 11 for a description of the synthesis of these compounds.

[a] *Benzopyran double bond is also saturated in this compound. Boxed compounds represent the most potent* FXR agonists.

FIG. 5

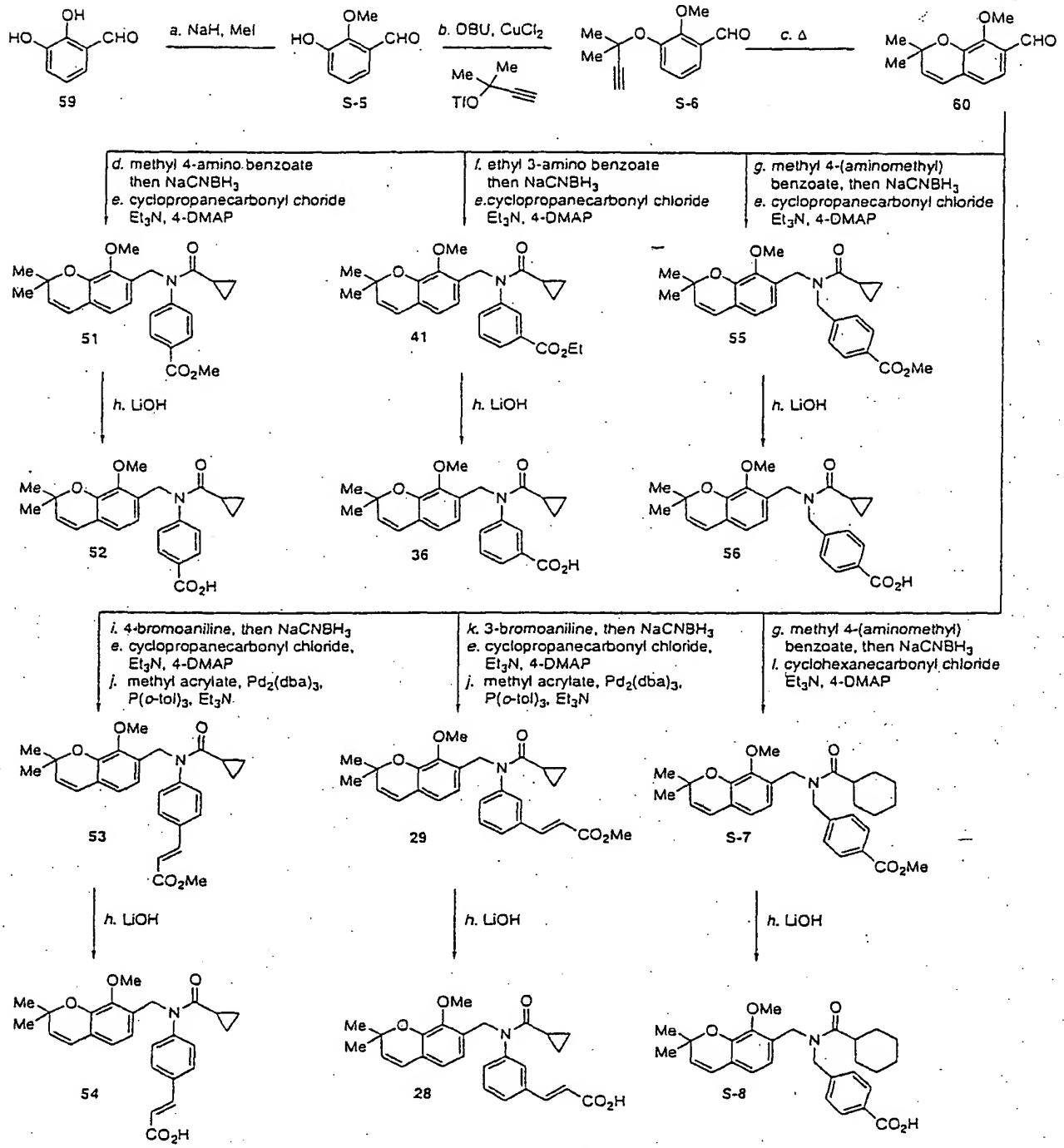
Representative procedure for the preparation of Region I-modified compounds: synthesis of methyl acrylate 29.[a]



[a]Reagents and conditions: (a) see reference 28; (b) 1.5 of equiv 2-methyl-3-butyn-2-ol, 1.5 equiv of DBU, 1.7 equiv trifluoroacetic anhydride, 0.1 equiv of $CuCl_2$, CH_3CN 0 → 25°C,12 h, 75%; (c) *N,N*-diethylaniline, 190°C, 0.5 h, 90%; (d) 1.5 equiv of 3-bromoaniline, THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 83%; (e) 1.3 equiv of cyclopropanecarbonyl chloride, 1.3 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 12 h, 85-95%; (f) 4.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.5 equiv of $P(o\text{-tol})_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 80%.

FIG. 6

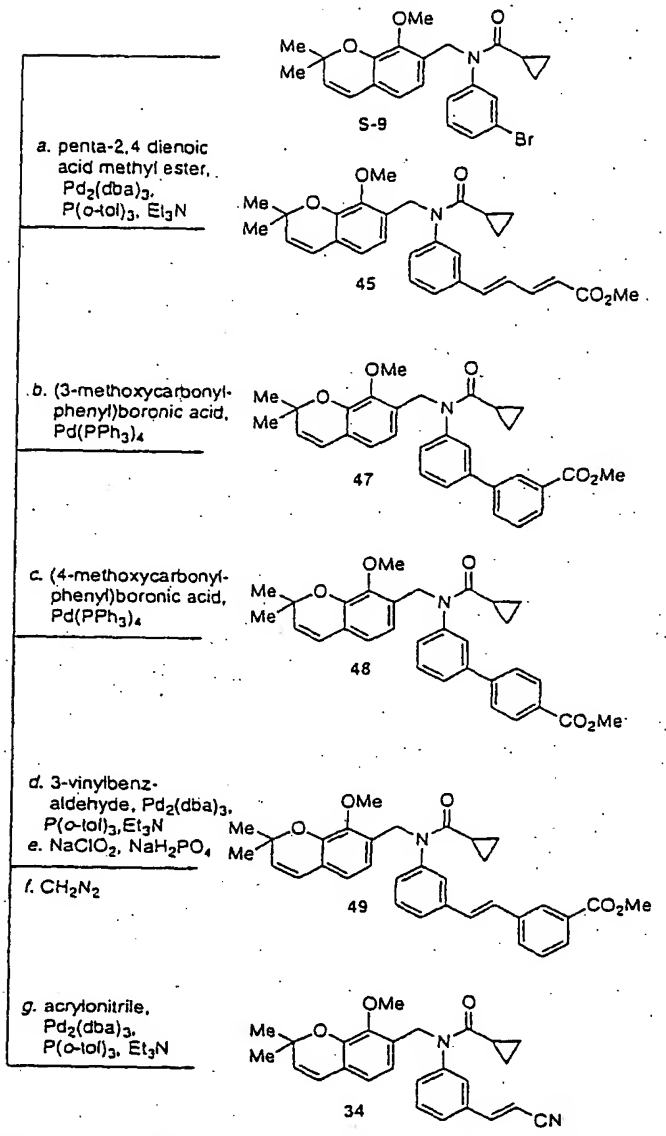
Solution phase synthesis of ester and acid containing compounds (SAR region I).[a]



[a]Reagents and conditions: (a) see reference 28; (b) 1.5 equiv of 2-methyl-3-butyn-2-ol, 1.5 equiv of DBU, 1.7 equiv of trifluoroacetic anhydride, 0.1 equiv of $CuCl_2$, CH_3CN 0 → 25°C,12 h, 75%; (c) *N,N*-diethylaniline, 190°C, 0.5 h, 90%; (d) 1.5 equiv of methyl 4-aminobenzoate, THF, 70°C,4 h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4 h, 82%; (e) 1.3 equiv of cyclopropanecarbonyl chloride, 1.3 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 12 h, 85-95%; (f) 1.5 equiv of ethyl 3-aminobenzoate, THF , 70°C, 4 h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 77%; (g) 1.5 equiv of methyl 4-(aminomethyl)benzoate,THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$,10% MeOH, 70°C, 4h, 80% ; (h) 4.0 equiv of LiOH, THF:H_2O (10:1), 25°C, 12 h, 75-98%; (i) 1.5 equiv of 4-bromoaniline, THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 78%; (j) 4.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.5 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 71-80%; (k) 1.5 equiv of 3-bromoaniline, THF, 70°C, 4h; then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4h, 83%; (l) 1.3 equiv of cyclohexanecarbonyl chloride, 1.3 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 12 h, 95%.

FIG 7

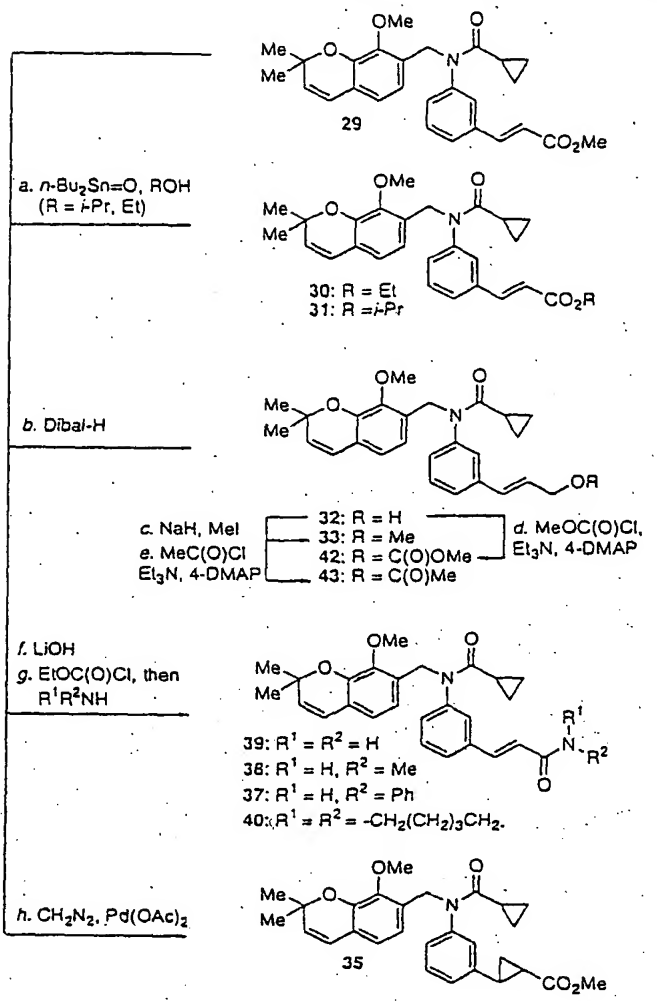
Solution phase synthesis of various ester and vinyl cyanide containing compounds via palladium catalyzed reaction manifolds (SAR region I).[a]



[a]Reagents and conditions: (a) 2.0 equiv of penta-2,4dienoic acid methyl ester, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of $P(o\text{-}tol)_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 70%; (b) 5.0 equiv of 3-(methoxycarbonylphenyl)boronic acid, toluene:MeOH:1M Na_2CO_3 (10:3:1), 90°C, 24 h, 75%;(c) 5.0 equiv of 4-(methoxycarbonylphenyl)boronic acid, toluene:MeOH:1M Na_2CO_3 (10:3:1), 90°C, 24 h, 78%; (d) 2.0 equiv of 3-vinylbenzaldehyde, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of $P(o\text{-}tol)_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 85%; (e) 1.5 equiv of $NaClO_2$, 4.0 equiv of NaH_2PO_4 , 10.0 equiv of 2-methyl-2-butene, THF:*t*-BuOH:H_2O (3:1:1), 25 °C, 3 h, 98% ; (f) 10 equiv of CH_2N_2, Et_2O, 0°C, 1 h, 100%; (g) 2.0 equiv of acrylonitrile, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of $P(o\text{-}tol)_3$, 5.0 of Et_3N, DMF, 90°C, 24h, 55%.

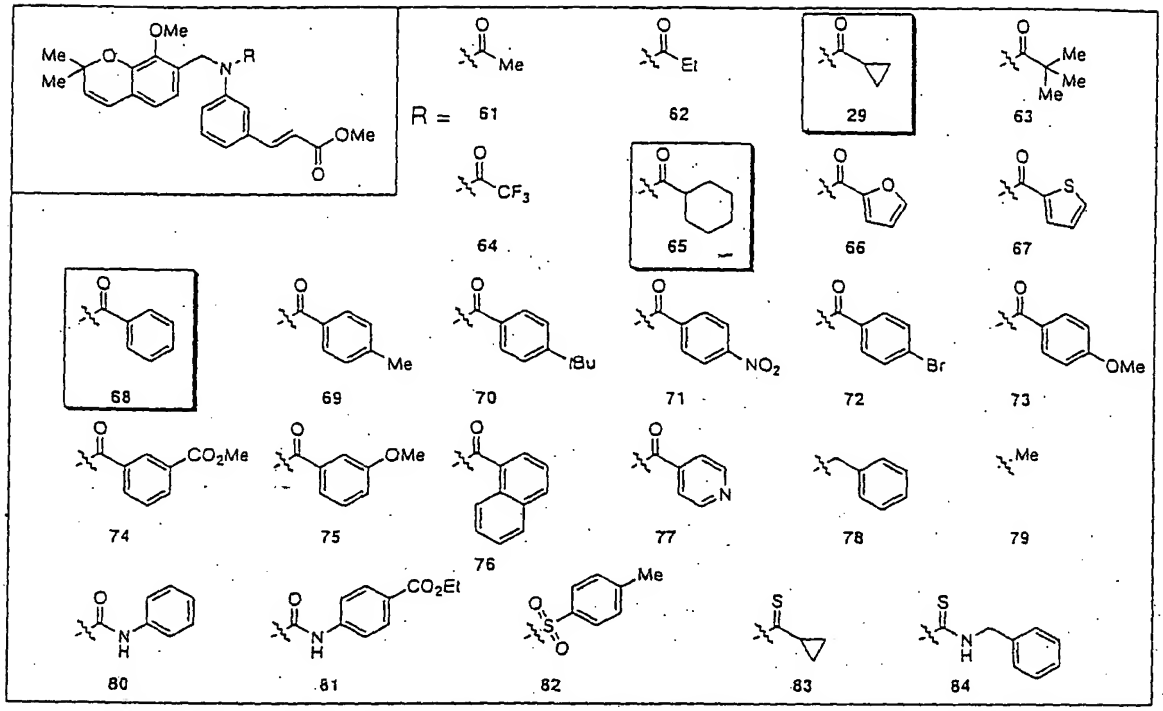
FIG. 8

Solution phase synthesis of ester modifications (SAR region I).[a]



[a]Reagents and conditions: (a) 0.5 equiv of n-Bu_2Sn=O, EtOH or i-PrOH, 25°C, 48 h, 50% and 34%, respectively; (b) 1.2 equiv of diisobutylaluminum hydride, toluene, -78°C, 0.5 h, 52%; (c) 2.0 equiv of NaH, 3.0 equiv of MeI, 0°C, 1 h, 95%; (d) 1.2 equiv of MeOC(O)Cl, 2.0 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 88%; (e) 1.2 equiv of MeC(O)Cl, 2.0 of equiv Et_3N, 0.1 of equiv 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (f) 4.0 equiv of LiOH, THF:H_2O (10:1), 25°C, 12h, 90%; (g) 1.2 equiv of EtOC(O)Cl, 1.5 equiv of Et_3N, CH_2Cl_2, 25°C,1 h, then 3.0 equiv of amine, CH_2Cl_2, 25°C,12 h, 85-95%; (h) 10.0 equiv of CH_2N_2, 0.2 of equiv $Pd(OAc)_2$, Et_2O, 25°C, 12 h, 95%.

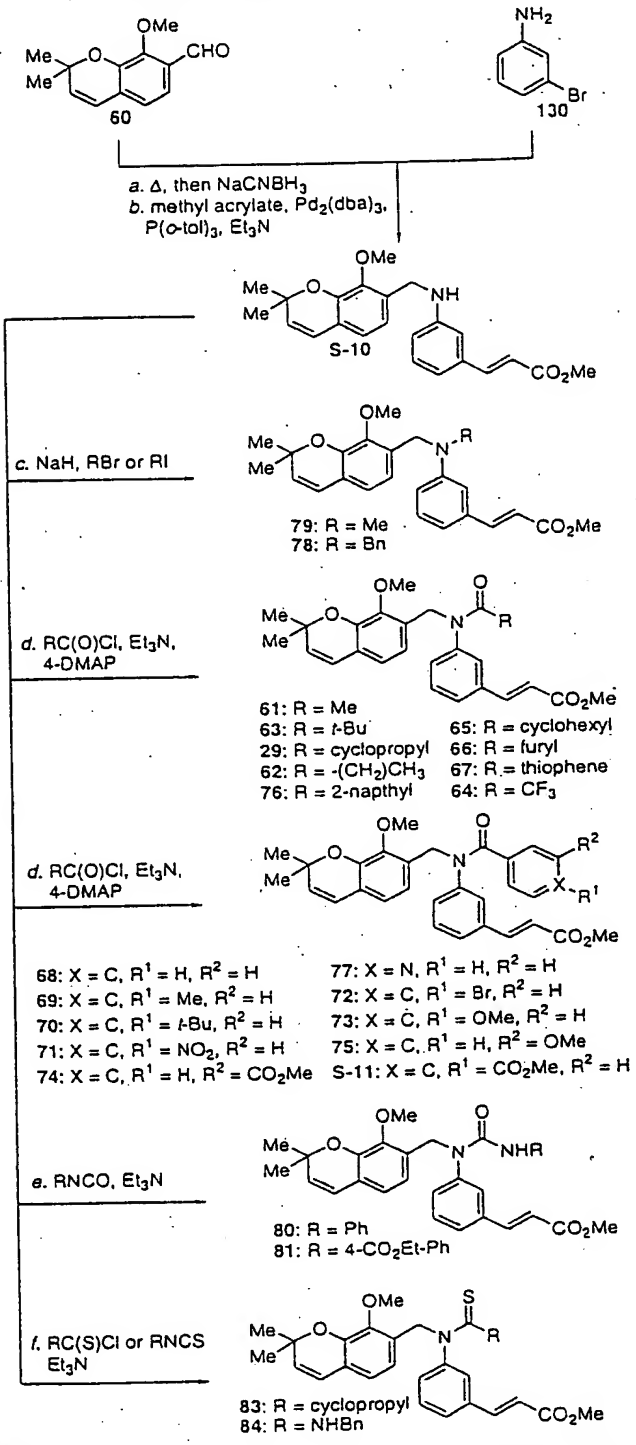
FIG. 9



Examination of the acyl group (region II) SAR. See Figure 11 for a description of the synthesis of these compounds. Boxed compounds are the most active FXR agonists

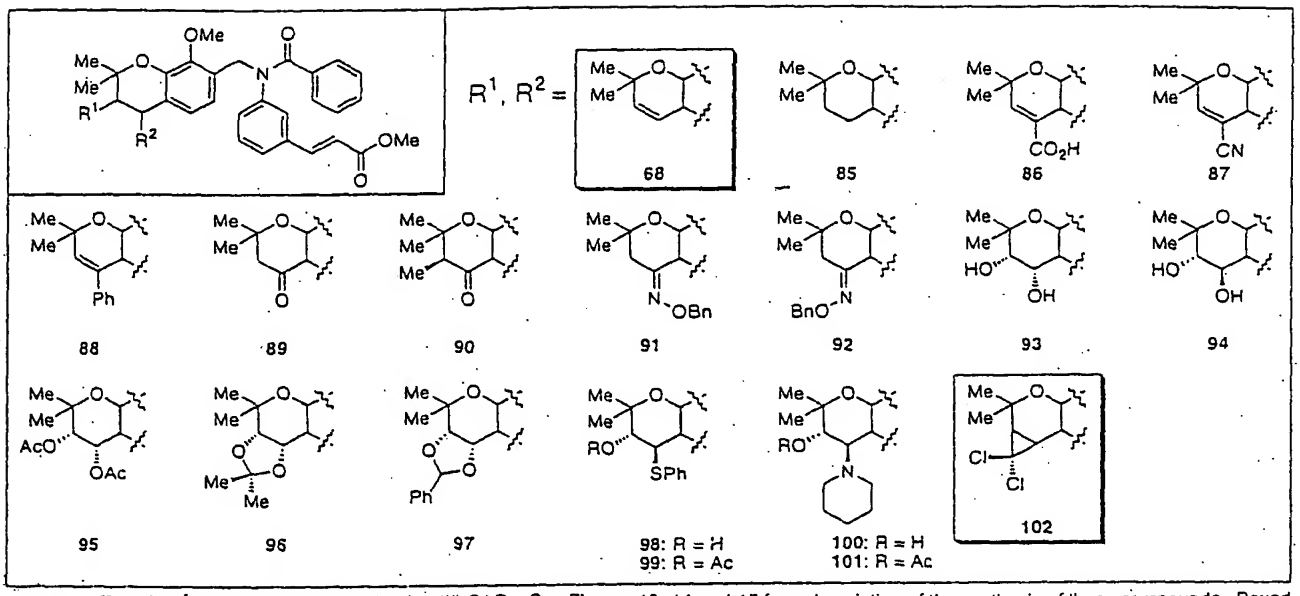
FIG. 10

. Solution phase synthesis of acyl group variants containing the acrylate moiety (SAR region II).[a]



[a]Reagents and conditions: (a) 1.0 equiv of 60, 2.0 equiv of 130, THF, 70°C, 4 h, then 2.0 equiv of $NaCNBH_3$, 10% MeOH, 70°C, 4 h, 70%; (b) 1.5 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.5 equiv of P(*o*-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 12 h, 65%; (c) 5.0 equiv of $NaHCO_3$, 5.0 equiv of alkyl halide, EtOH, 80°C, 24 h, 70-85%; (d) 5.0 equiv of acid chloride, 5.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 55-100%; (e) 5.0 equiv of isocyanate, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 24 h, 75-85%; (f) 5.0 equiv of thioacid chloride or thioisocyanate, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 24h, 50-70%.

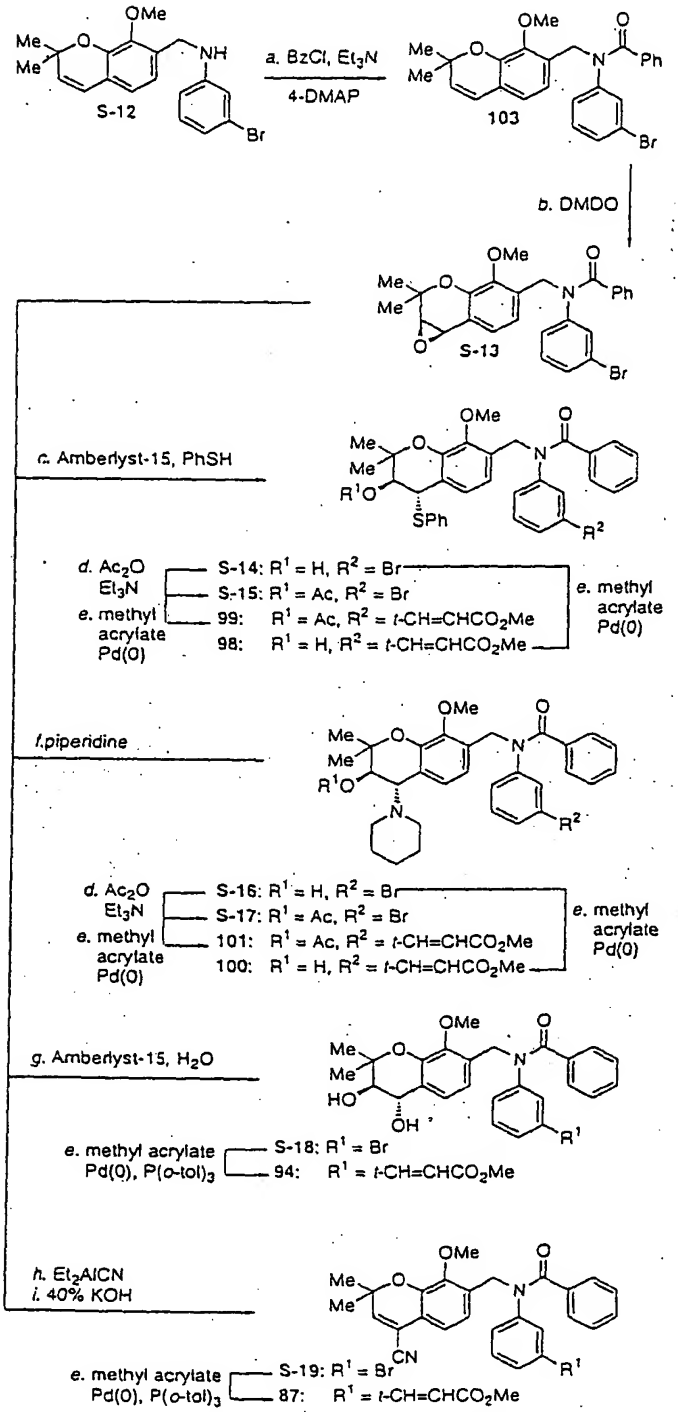
FIG. 11



Examination of the benzopyran (region III) SAR. See Figures 13, 14 and 15 for a description of the synthesis of these compounds. Boxed compounds are the most active FXR agonists.

FIG. 12

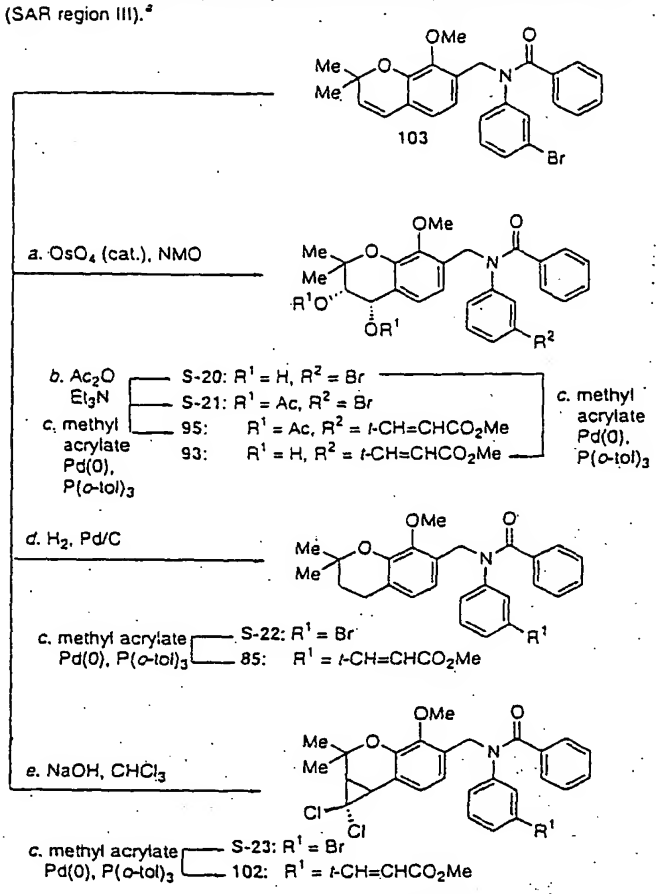
Solution phase synthesis of benzopyran olefin modifications (SAR region III).[a]



[a]Reagents and conditions: (a) 2.0 equiv of benzoyl chloride, 2.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 95%; (b) 10 equiv of DMDO, acetone, 0°C, 1 h, 100%; (c) 5.0 equiv of PhSH, Amberlyst-15 (cat.), CH_2Cl_2, 25°C, 24 h; 95%; (d) 2.0 equiv of acetic anhydride, 2.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (e) 2.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(o-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 70-84%; (f) 5.0 equiv of piperidine, CH_2Cl_2, 25°C, 48h, 65%; (g) 5.0 equiv of H_2O, Amberlyst-15 (cat.), THF , 25°C, 24 h, 95%; (h) 2.0 equiv of Et_2AlCN, CH_2Cl_2, 0°C, 1 h, 83%; (i) 40% KOH:MeOH (1:2), 25°C,24 h, 90%.

FIG. 13

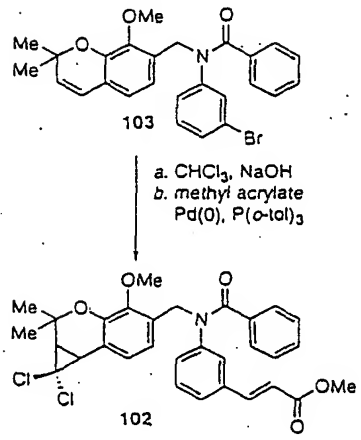
Solution phase synthesis of benzopyran olefin modifications (SAR region III).[a]



[a]Reagents and conditions: (a) 0.02 equiv of OsO_4, 2.0 equiv of NMO, acetone:H_2O (10:1), 25°C, 24 h, 85%; (b) 5.0 of equiv acetic anhydride, 10.0 equiv of Et_3N, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25°C, 24 h, 90%; (c) 2.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of $P(o\text{-tol})_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 65-80%; (d) 10% Pd/C, EtOAc, 25°C, 0.5 h, 100% (e) $CHCl_3$:50% NaOH (7:1), adogen 464 (cat.) 25°C, 6 h, 85%.

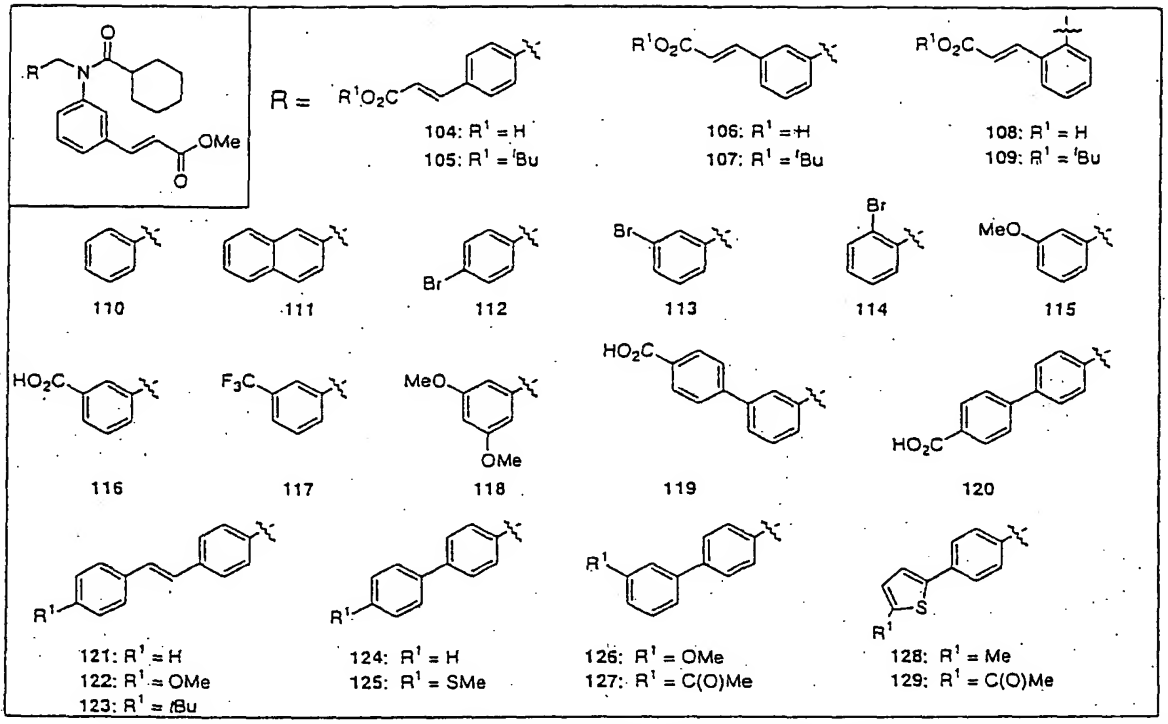
FIG. 14

. Synthesis of compound 102. Exploration of region III SAR.[a]



[a]Reagents and conditions: (a) $CHCl_3$:50% NaOH (7:1), adogen 464 (cat.) 25°C, 6 h, 85%; (b) 2.0 equiv of methyl acrylate, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(o-tol)$_3$, 5.0 equiv of Et_3N, DMF, 90°C, 24 h, 75%.

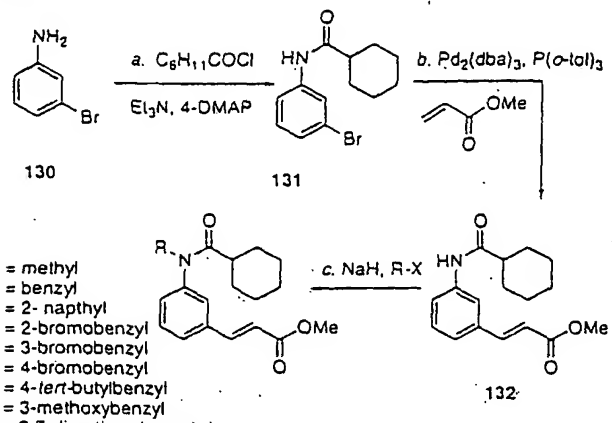
FIG. 15



Examination of the benzopyran replacement (region III) SAR. See Figures 17, 18, 20 and 24 for a description of the synthesis of these compounds.

FIG. 16

Solution phase synthesis of region III analogs: replacement of the benzopyran.[a]

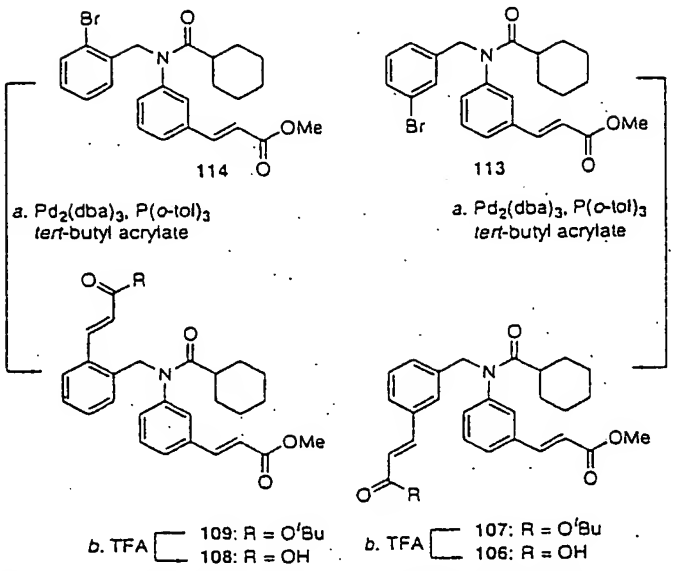


147: R = methyl
110: R = benzyl
111: R = 2- napthyl
114: R = 2-bromobenzyl
115: R = 3-bromobenzyl
116: R = 4-bromobenzyl
148: R = 4-*tert*-butylbenzyl
115: R = 3-methoxybenzyl
118: R = 3,5-dimethoxybenzyl
117: R = 3-(trifluromethyl)benzyl

[a]Reagents and conditions: (a) 1.1 equiv of $C_6H_{11}COCl$, 1.3 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 3 h, 95%; (b) 4.0 equiv of methyl acrylate, 5.0 equiv of Et_3N, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of $P(o\text{-}tol)_3$, DMF, 90°C, 12 h, 80% ; (c) 1.1 equiv of NaH, THF, 0 °C, 30 min; then 1.3 equiv of benzyl bromides, THF, 0°C, 2 h, 60 - 90%. R-X = methyl iodide, benzyl bromide, 2-bromobenzyl bromide, 3-bromobenzyl bromide, 4-bromobenzyl bromide, 4-*tert*-butylbenzyl bromide, 3-methoxybenzyl bromide, 3,5-dimethoxybenzyl bromide, 3-(trifluromethyl)benzyl bromide, 2-napthyl bromide.

FIG. 17

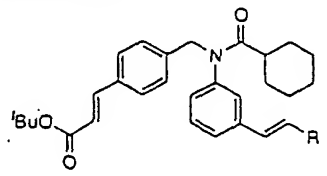
Solution phase synthesis of derivatives region III .[a]



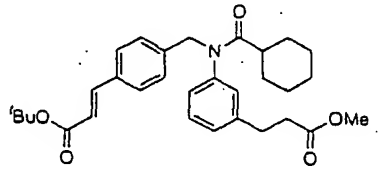
[a]Reagents and conditions: (a) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 80%; (b) 20% TFA in CH_2Cl_2, 25°C, 1 h, 95%.

FIG. 18

a. SAR of region I

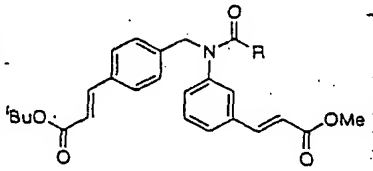


	R	EC_{50} (nM)	RE[a]
105	COOMe	127	2.12
133	COOEt	256	2.07
134	COO^{t}Bu	>1000	1.06
135	$CONH_2$	>1000	0.50
136	CH_2OMe	243	1.68
137	CH_2OEt	220	1.74
138	CH_2OPh	2830	0.45



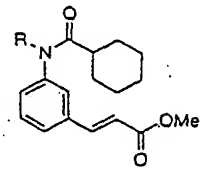
139: EC_{50} = 274 nM
RE[a] = 1.38

b. SAR of region II

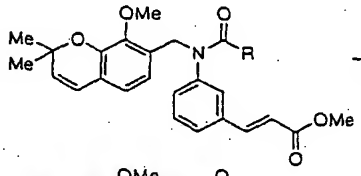


	R	EC_{50} (nM)	RE[a]
140	cyclopropyl	250	1.68
141	cyclobutyl	187	1.84
142	cyclopentyl	162	2.16
105	cyclohexyl	127	2.12
143	phenyl	236	1.96
144	2-furyl	205	1.93
145	isopropylamino	212	1.96
146	benzylamino	>1000	0.27

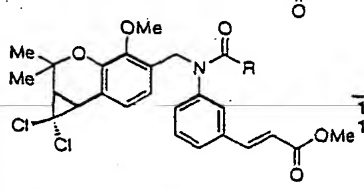
c. SAR of region III



	R	EC_{50} (nM)	RE[a]
132	H	>1000	0.09
147	methyl	>1000	0.09
110	benzyl	>1000	0.09
111	2- napthyl	680	0.41
114	2-bromobenzyl	>1000	0.11
113	3-bromobenzyl	>1000	0.10
112	4-bromobenzyl	>1000	0.28
148	4-*tert*-butylbenzyl	>1000	0.15
115	3-methoxybenzyl	>1000	0.11
118	3,5-dimethoxybenzyl	606	0.11
117	3-(trifluromethyl)benzyl	>1000	0.12

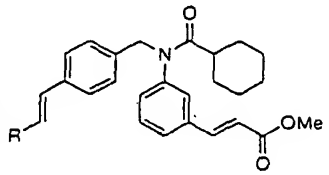


	R	EC_{50} (nM)	RE[a]
68	phenyl	>1000	0.83
65	cyclohexyl	358	0.40

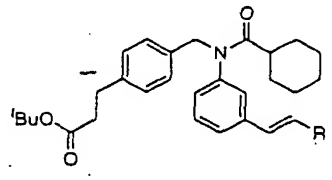


	R	EC_{50} (nM)	RE[a]
102	phenyl	333	0.64
149	cyclohexyl	188	0.50

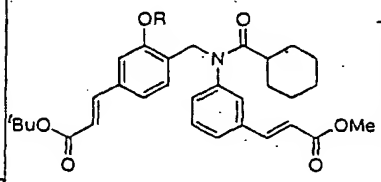
d. SAR of region III



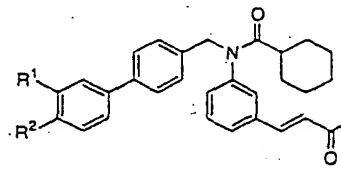
	R	EC_{50} (nM)	RE[a]
104	COOH	>1000	0.08
150	COOMe	>1000	0.87
151	COOEt	>1000	1.14
152	COO^{i}Pr	163	1.97
105	COO^{t}Bu	127	2.12
153	COOBn	>1000	0.23
154	$CONMe_2$	>1000	0.66
155	CONH^{t}Bu	>1000	1.65
156	CH_2OMe	233	1.63
157	CH_2OEt	198	2.06
158	CH_2OPh	>1000	0.64



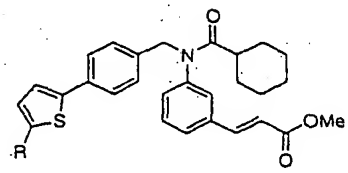
	R	EC_{50} (nM)	RE[a]
159	COOMe	240	1.56
160	COO^{t}Bu	>1000	0.64



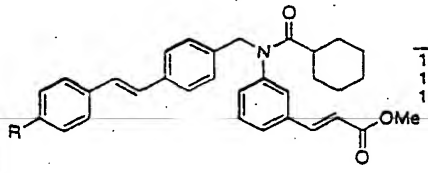
	R	EC_{50} (nM)	RE[a]
161	H	> 1000	0.12
162	Me	> 1000	0.14
163	Bn	> 1000	0.38
164	MeC(O)	> 1000	0.16
165	$C_6H_5C(O)$	> 1000	0.16
166	$MeS(O_2)$	> 1000	0.18
167	$EtOOCCH_2$	> 1000	0.18



	R^1	R^2	EC_{50} (nM)	RE[a]
[illegible]	OMe	H	77	1.51
127	C(O)Me	H	227	1.30
125	H	SMe	69	1.74
124	H	H	510	0.71



	R	EC_{50} (nM)	RE[a]
128	Me	206	1.78
129	C(O)Me	256	1.48

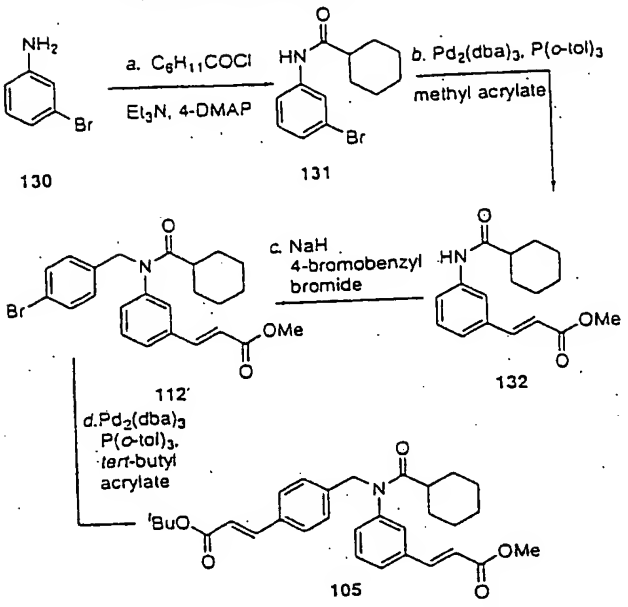


	R	EC_{50} (nM)	RE[a]
121	H	36	1.55
122	OMe	208	1.67
123	*t*-Bu	>1000	0.29

Panel a) Highlights of region I SAR. Panel b) Highlights of region II SAR in the bis-cinnimate series. Panel c) Effects of benzopyran substitution. Panel d) Highlights of region III SAR including the bis-cinnamate, styryl and biaryl series. Values represent the mean of at least four experiments. [a]RE = relative efficacy of the indicated compound at 1μM to 100 μM CDCA .

FIG. 19

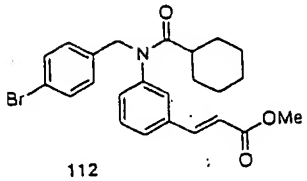
Preparation of bis-cinnamate 105.[a]



[a]Reagents and conditions: (a) 1.1 equiv of $C_6H_{11}COCl$, 1.3 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 3 h, 95%;(b) 4.0 equiv of methyl acrylate, 5.0 equiv of Et_3N, 0.2 equiv of $Pd_2(dba)_3$, 0.6 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 80%;(c) 1.1 equiv of NaH, THF, 0 °C, 30 min; then 1.3 equiv of 4-bromobenzylbromide, THF, 0°C, 2 h, 90%;(d) 4.0 equiv of acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of P(*o*-tol)$_3$, DMF, 90°C, 12 h, 75%.

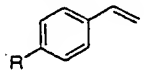
FIG. 20

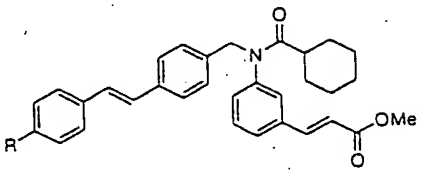
Synthesis of region III modifications; cinnamate substitutions.[a]



112

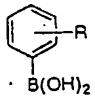
a. $Pd_2(dba)_3$
$P(o\text{-tol})_3$

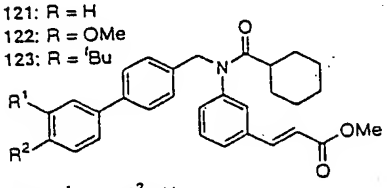




121: R = H
122: R = OMe
123: R = ^{t}Bu

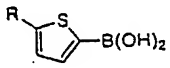
b. $Pd(PPh_3)_4$
$P(o\text{-tol})_3$

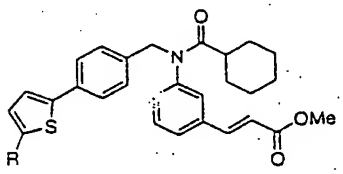




124: R^1 = H, R^2 = H
125: R^1 = H, R^2 = SMe
126: R^1 = OMe, R^2 = H
127: R^1 = C(O)Me, R^2 = H

b. $Pd(PPh_3)_4$



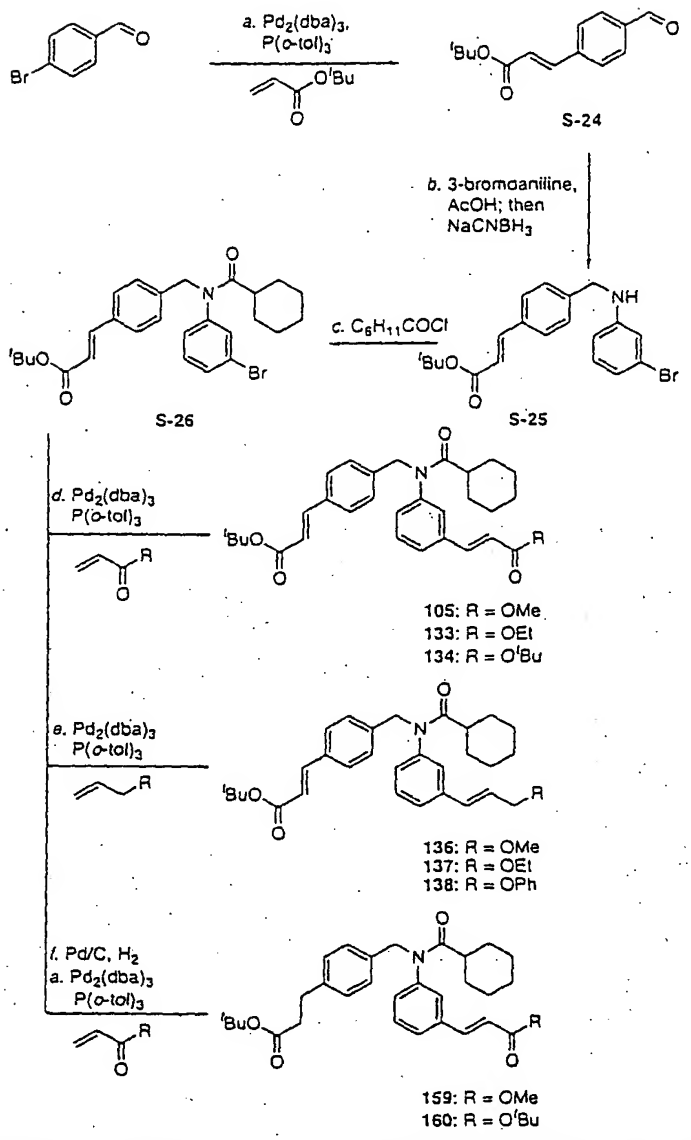


128: R = Me
129: R = C(O)Me

[a]Reagents and conditions: (a) 4.0 equiv of styrene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-tol})_3$, DMF, 90°C, 12 h, 65 - 80% ; (b) 2.5 equiv of boronic acid, 0.2 equiv of $Pd(PPh_3)_4$, toulene:MeOH:1 M Na_2CO_3 (10:3:1), 80°C, 12 h, 60 - 80%.

FIG. 21

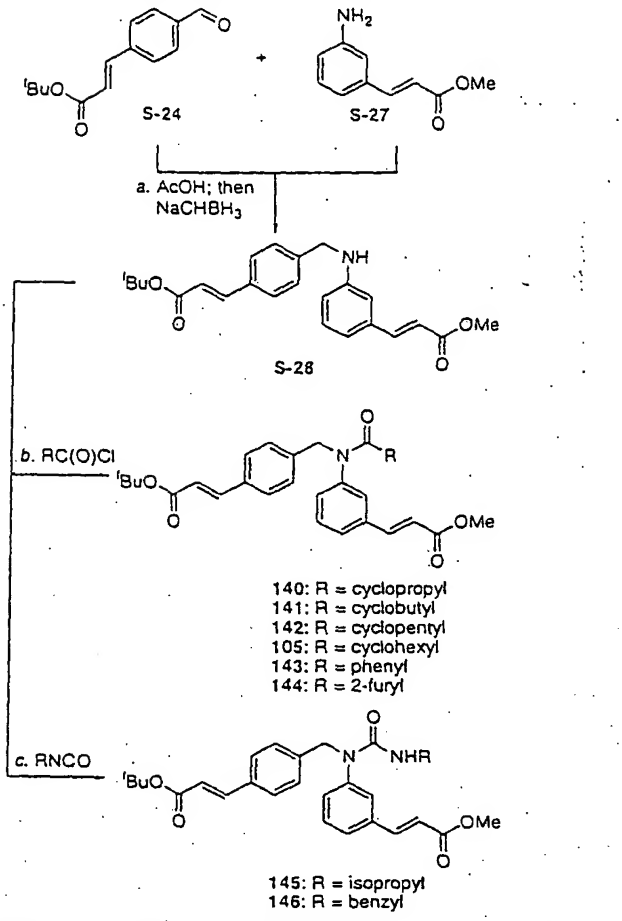
Synthesis of region I/region III cinnamate modifications.[a]



[a]Reagents and conditions: (a) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-tol})_3$, DMF, 90°C, 12 h, 85%;(b) 1.5 equiv of 3-bromoaniline, 0.05 equiv of AcOH, MeOH, 25°C, 30 min; then 1.7 equiv of $NaCNBH_3$, 1 h, 90%; (c) 1.1 equiv of $C_6H_{11}COCl$, 1.3 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 3 h, 90%; (d) 4.0 equiv of acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-tol})_3$, DMF, 90°C, 12 h, 60 - 85%;(e) 4.0 equiv of alkene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-tol})_3$, DMF, 90°C, 12 h, 35 - 80%; (f) 0.05 equiv of Pd/C, H_2 (1 atm), EtOAc, 25°C, 30 min, 100 %.

FIG. 22

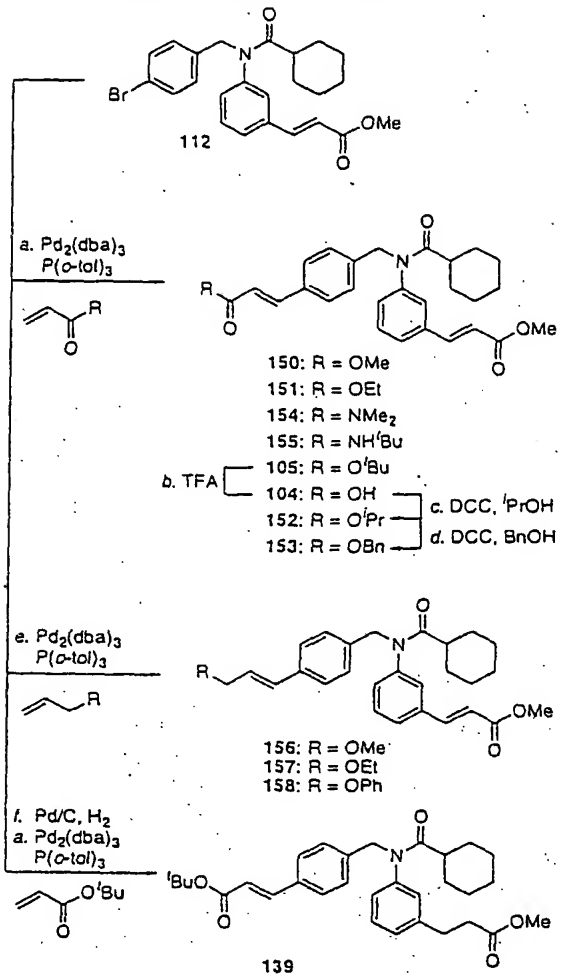
Synthesis of acyl group analogs in the bis cinnamate series.[a]



[a]Reagents and conditions: (a) 1.0 equiv of S-24, 1.0 equiv of S-27, 0.05 equiv of AcOH, MeOH, 25°C, 30 min; then 1.2 equiv of $NaCNBH_3$, 25°C, 1 h, 85%; (b) 2.0 equiv of acid chloride, 3.0 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 1 h, 80 - 95%; (c) 2.0 equiv of isocyanate, 3.0 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 1 h, 60 - 80%.

FIG. 23

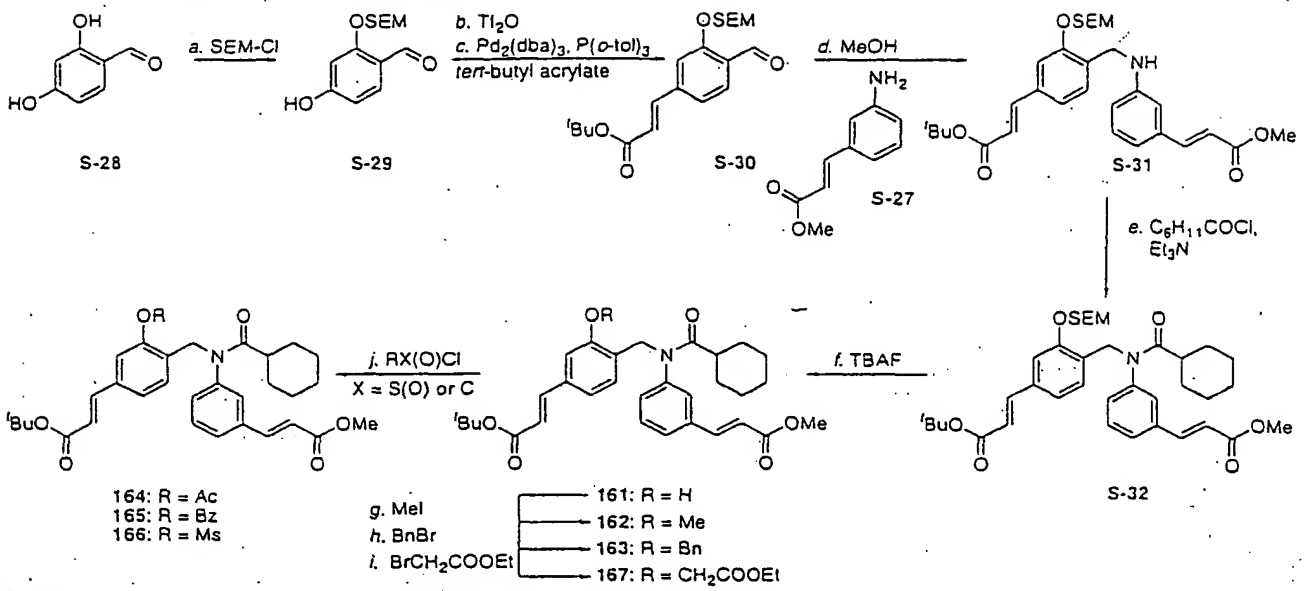
Synthesis of region III cinnimate modifications .



[a]Reagents and conditions: (a) 4.0 equiv of acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-}tol)_3$, DMF, 90°C, 12 h, 50 - 80% ; (b) 20% TFA in CH_2Cl_2, 1 h, 25°C, 95%; (c) 1.2 equiv of DCC, 10.0 equiv of ^{i}PrOH, 0.2 equiv of 4-DMAP, DMF, 25°C, 12 h, 60%; (d) 1.2 equiv of DCC, 10.0 equiv of BnOH, 0.2 equiv of 4-DMAP, DMF, 25°C, 12 h, 60%;(e) 4.0 equiv of alkene, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-}tol)_3$, DMF, 90°C, 12 h, 35 - 75%; (f) 0.05 equiv of Pd/C, H_2 (1 atm), EtOAc, 25°C, 30 min, 100 %.

FIG. 24

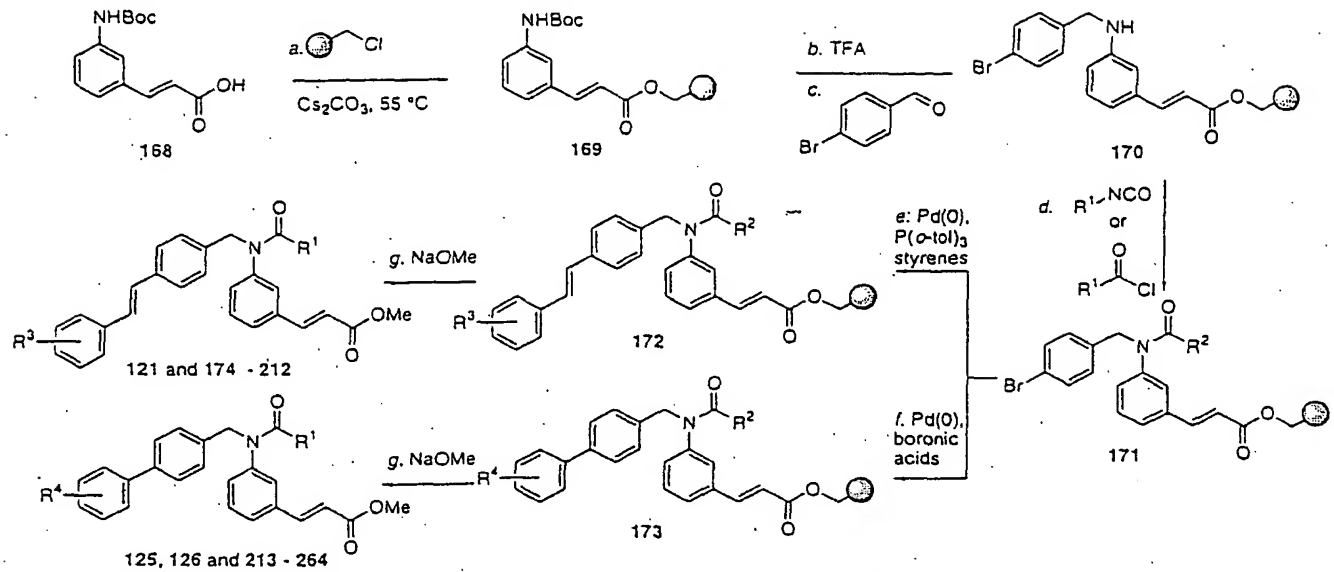
Synthesis of region III ring analogs.[a]



[a]Reagents and conditions: (a) 1.0 equiv of SEM-Cl, 1.2 equiv of Et_3N, CH_2Cl_2, 25°C, 12 h, 75%; (b) 1.05 equiv of Tf_2O, 1.2 equiv of Et_3N, CH_2Cl_2, -78°C, 1 h, 95%; (c) 4.0 equiv of *tert*-butyl acrylate, 5.0 equiv of Et_3N, 0.05 equiv of $Pd_2(dba)_3$, 0.15 equiv of $P(o\text{-tol})_3$, 90°C, 12 h, 76%; (d) 1.2 equiv of S-27, 0.05 equiv of AcOH, MeOH, 25°C, 1 h; then 1.5 equiv of $NaCNBH_3$, 2 h, 80%; (e) 1.2 equiv of $C_6H_{11}COCl$, 1.5 equiv of Et_3N, 0.05 equiv of 4-DMAP, CH_2Cl_2, 25°C, 4 h, 90%; (f) 7.0 equiv of TBAF, THF:HMPA (9:1), 55°C, 12 h, 65%; (g) 3.0 equiv of MeI, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 90%; (h) 3.0 equiv of BnBr, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 65%; (i) 3.0 equiv of $BrCH_2COOEt$, 5.0 equiv of K_2CO_3, DMF, 80°C, 12 h, 85%; (j) 3.0 equiv of AcCl, BzCl or MsCl, 5.0 equiv of Et_3N, CH_2Cl_2, 25°C, 2 h, 70-90%.

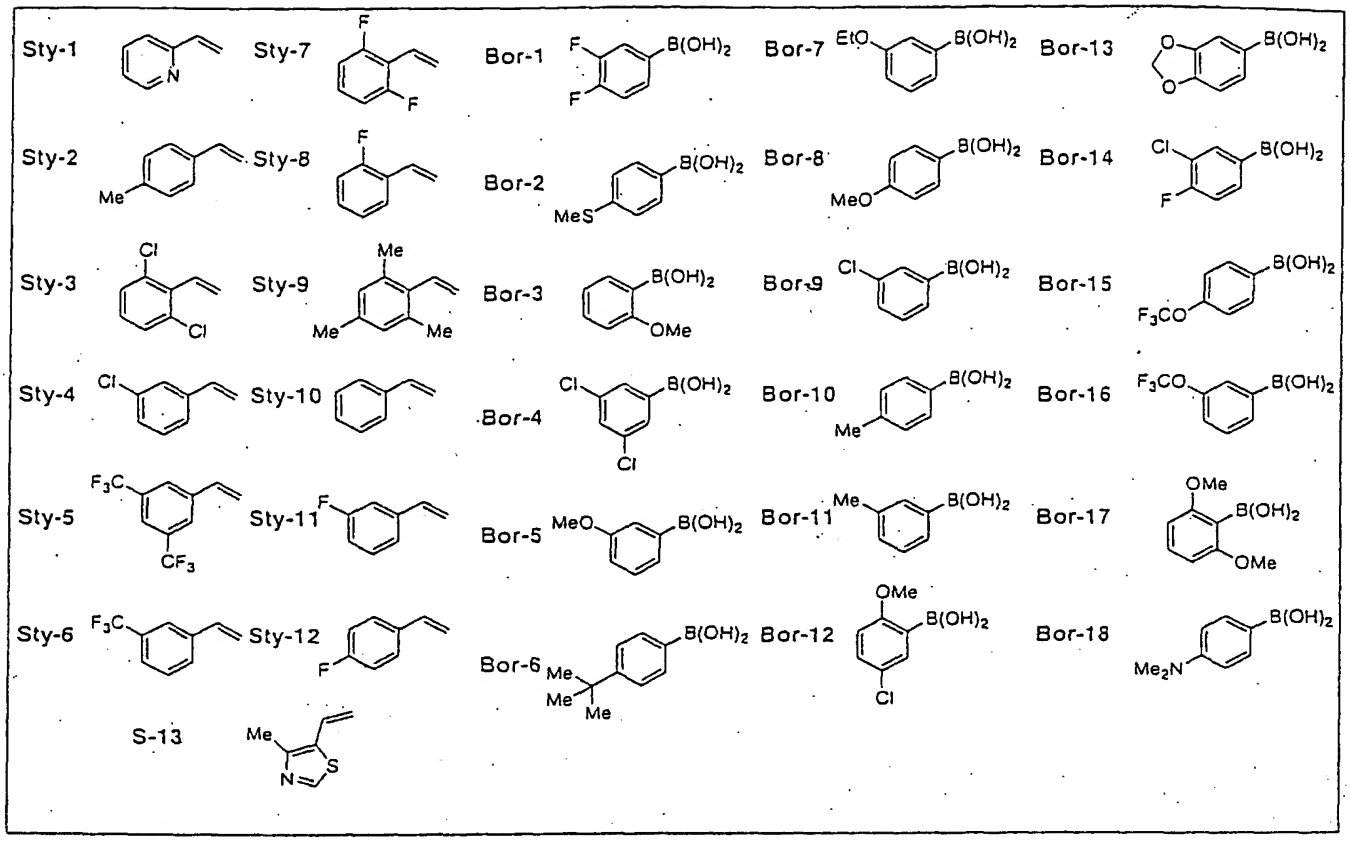
FIG. 25

Solid phase synthesis of focused libraries of biaryl and stilbene cinnamates.[a]



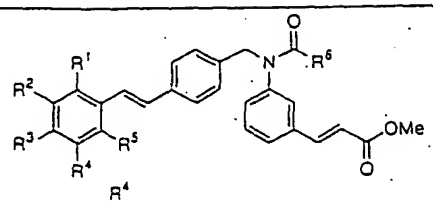
[a]Reagents and conditions: (a) 2.0 equiv of 168, 1.0 equiv of Merrifield Resin (0.91 mmol/g), 2.0 equiv of Cs_2CO_3, 0.5 equiv of TBAI, DMF, 55°C, 24 h; (b) 20% TFA in CH_2Cl_2, 25°C, 1 h; (c) 10.0 equiv of 4-bromobenzaldehyde, 0.05 equiv of AcOH, THF:MeOH (2:1), 25°C, 1 h; then, 8.0 equiv of $NaCNBH_3$, THF:MeOH (2:1), 25°C, 2 h; (d) *for* R^1COCl: 30.0 *equiv of* R^1COCl, 40.0 *equiv of* Et_3N, 1.0 *equiv of* 4-DMAP, CH_2Cl_2, 25°C, 12 h; *for* R^1NCO, 30.0 equiv of R^1NCO, 40.0 equiv of Et_3N, 1.0 equiv of 4-DMAP, DMF, 65°C, 60 h; (e) 8.0 equiv of styrene, 10.0 equiv of Et_3N, 0.5 equiv of $Pd_2(dba)_3$, 1.5 equiv of P(o-tol)$_3$, DMF, 90°C, 48 h; (f) 5.0 equiv of boronic acid, 3.0 equiv Cs_2CO_3, 0.5 equiv of $Pd(PPh_3)_4$, DMF, 90°C, 24 h; (g) 10.0 *equiv of* NaOMe, Et_2O:MeOH (10:1), 25°C, 20 *min*.

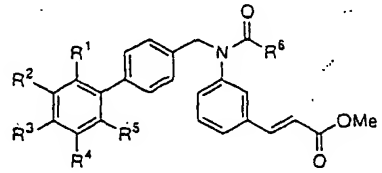
FIG. 26



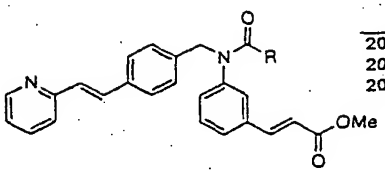
Structures of styrenes and boronic acids used in library construction. See Figure 26 and text for discussion.

FIG. 27

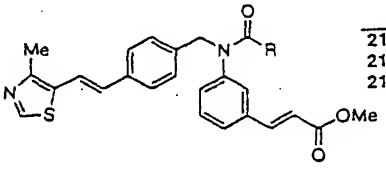




	R^1	R^2	R^3	R^4	R^5	R^6	EC_{50} (nM)	RE[a]
174	H	H	Me	H	H	$-C_6H_{11}$	342	0.83
175	H	H	Me	H	H	$-CH(CH_3)_2$	1410	0.37
176	H	H	Me	H	H	$-NHCH(CH_3)_2$	3570	0.10
177	Cl	H	H	H	Cl	$-C_6H_{11}$	150	0.12
178	Cl	H	H	H	Cl	$-CH(CH_3)_2$	195	0.14
179	Cl	H	H	H	Cl	$-NHCH(CH_3)_2$	216	0.15
180	H	Cl	H	H	H	$-C_6H_{11}$	165	1.41
181	H	Cl	H	H	H	$-CH(CH_3)_2$	164	1.09
182	H	Cl	H	H	H	$-NHCH(CH_3)_2$	339	0.59
183	H	CF_3	H	CF_3	H	$-C_6H_{11}$	1470	0.15
184	H	CF_3	H	CF_3	H	$-CH(CH_3)_2$	1950	0.13
185	H	CF_3	H	CF_3	H	$-NHCH(CH_3)_2$	1830	0.13
186	H	CF_3	H	H	H	$-C_6H_{11}$	937	0.35
187	H	CF_3	H	H	H	$-CH(CH_3)_2$	267	0.70
188	H	CF_3	H	H	H	$-NHCH(CH_3)_2$	932	0.31
189	F	H	H	H	F	$-C_6H_{11}$	174	0.94
190	F	H	H	H	F	$-CH(CH_3)_2$	108	0.79
191	F	H	H	H	F	$-NHCH(CH_3)_2$	4020	0.21
192	F	H	H	H	H	$-C_6H_{11}$	64	1.41
193	F	H	H	H	H	$-CH(CH_3)_2$	70	1.17
194	F	H	H	H	H	$-NHCH(CH_3)_2$	431	0.69
195	Me	H	Me	H	Me	$-C_6H_{11}$	518	0.24
196	Me	H	Me	H	Me	$-CH(CH_3)_2$	149	0.30
197	Me	H	Me	H	Me	$-NHCH(CH_3)_2$	431	0.14
121	H	H	H	H	H	$-C_6H_{11}$	36	1.55
198	H	H	H	H	H	$-CH(CH_3)_2$	65	1.33
200	H	H	H	H	H	$-NHCH(CH_3)_2$	119	1.38
201	H	F	H	H	H	$-C_6H_{11}$	86	1.36
202	H	F	H	H	H	$-CH(CH_3)_2$	71	1.33
203	H	F	H	H	H	$-NHCH(CH_3)_2$	467	0.61
204	H	H	F	H	H	$-C_6H_{11}$	185	0.53
205	H	H	F	H	H	$-CH(CH_3)_2$	120	1.19
206	H	H	F	H	H	$-NHCH(CH_3)_2$	348	0.91



	R	EC_{50} (nM)	RE[a]
207	$-C_6H_{11}$	309	0.81
208	$-CH(CH_3)_2$	310	0.62
209	$-NHCH(CH_3)_2$	575	0.66

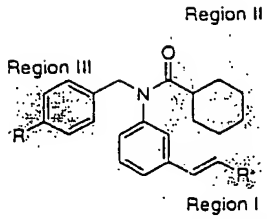


	R	EC_{50} (nM)	RE[a]
210	$-C_6H_{11}$	227	0.53
211	$-CH(CH_3)_2$	228	0.32
212	$-NHCH(CH_3)_2$	366	0.42

	R^1	R^2	R^3	R^4	R^5	R^6	EC_{50} (nM)	RE[a]
213	H	F	F	H	H	$-C_6H_{11}$	72	1.70
214	H	F	F	H	H	$-CH(CH_3)_2$	249	1.15
215	H	F	F	H	H	$-NHCH(CH_3)_2$	8180	0.23
125	H	H	SMe	H	H	$-C_6H_{11}$	69	1.74
216	H	H	SMe	H	H	$-CH(CH_3)_2$	51	0.98
217	H	H	SMe	H	H	$-NHCH(CH_3)_2$	178	0.23
218	OMe	H	H	H	H	$-C_6H_{11}$	359	0.49
219	OMe	H	H	H	H	$-CH(CH_3)_2$	377	0.28
220	OMe	H	H	H	H	$-NHCH(CH_3)_2$	4010	0.09
126	H	Cl	H	Cl	H	$-C_6H_{11}$	284	0.95
221	H	Cl	H	Cl	H	$-CH(CH_3)_2$	661	0.54
222	H	Cl	H	Cl	H	$-NHCH(CH_3)_2$	>10000	0.10
223	H	OMe	H	H	H	$-C_6H_{11}$	101	1.51
224	H	OMe	H	H	H	$-CH(CH_3)_2$	72	1.26
225	H	OMe	H	H	H	$-NHCH(CH_3)_2$	1370	0.41
226	H	OEt	H	H	H	$-C_6H_{11}$	147	1.37
227	H	OEt	H	H	H	$-CH(CH_3)_2$	173	1.03
228	H	OEt	H	H	H	$-NHCH(CH_3)_2$	2350	0.33
229	H	H	OMe	H	H	$-C_6H_{11}$	89	1.71
230	H	H	OMe	H	H	$-CH(CH_3)_2$	97	1.21
231	H	H	OMe	H	H	$-NHCH(CH_3)_2$	144	1.16
232	H	Cl	H	H	H	$-C_6H_{11}$	94	1.56
233	H	Cl	H	H	H	$-CH(CH_3)_2$	77	1.52
234	H	Cl	H	H	H	$-NHCH(CH_3)_2$	1400	0.49
235	H	H	Me	H	H	$-C_6H_{11}$	26	1.38
236	H	H	Me	H	H	$-CH(CH_3)_2$	118	1.48
237	H	H	Me	H	H	$-NHCH(CH_3)_2$	449	0.80
238	H	Me	H	H	H	$-C_6H_{11}$	109	1.43
239	H	Me	H	H	H	$-CH(CH_3)_2$	163	1.09
240	H	Me	H	H	H	$-NHCH(CH_3)_2$	1330	0.53
241	OMe	H	H	Cl	H	$-C_6H_{11}$	233	1.16
242	OMe	H	H	Cl	H	$-CH(CH_3)_2$	226	0.79
243	OMe	H	H	Cl	H	$-NHCH(CH_3)_2$	3080	0.17
244	H	$-OCH_2O-$		H	H	$-C_6H_{11}$	38	1.90
245	H	$-OCH_2O-$		H	H	$-CH(CH_3)_2$	19	1.25
246	H	$-OCH_2O-$		H	H	$-NHCH(CH_3)_2$	96	1.51
247	H	Cl	F	H	H	$-C_6H_{11}$	66	1.87
248	H	Cl	F	H	H	$-CH(CH_3)_2$	129	1.64
249	H	Cl	F	H	H	$-NHCH(CH_3)_2$	3050	0.41
250	H	H	OCF_3	H	H	$-C_6H_{11}$	264	1.04
251	H	H	OCF_3	H	H	$-CH(CH_3)_2$	219	0.78
252	H	H	OCF_3	H	H	$-NHCH(CH_3)_2$	7530	0.21
253	H	OCF_3	H	H	H	$-C_6H_{11}$	420	0.84
254	H	OCF_3	H	H	H	$-CH(CH_3)_2$	247	0.69
255	H	OCF_3	H	H	H	$-NHCH(CH_3)_2$	>10000	0.09
256	OMe	H	H	H	OMe	$-C_6H_{11}$	77	0.12
257	OMe	H	H	H	OMe	$-CH(CH_3)_2$	95	0.10
258	OMe	H	H	H	OMe	$-NHCH(CH_3)_2$	561	0.10
259	H	H	NMe_2	H	H	$-C_6H_{11}$	25	1.72
260	H	H	NMe_2	H	H	$-CH(CH_3)_2$	57	1.07
261	H	H	NMe_2	H	H	$-NHCH(CH_3)_2$	162	1.01
262	H	H	*t*-Bu	H	H	$-C_6H_{11}$	132	1.38
263	H	H	*t*-Bu	H	H	$-CH(CH_3)_2$	343	0.59
264	H	H	*t*-Bu	H	H	$-NHCH(CH_3)_2$	262	1.02

Activities of stilbene and biaryl series. [a]RE = relative efficacy of the indicated compound at 1μM to 100 μM CDCA .

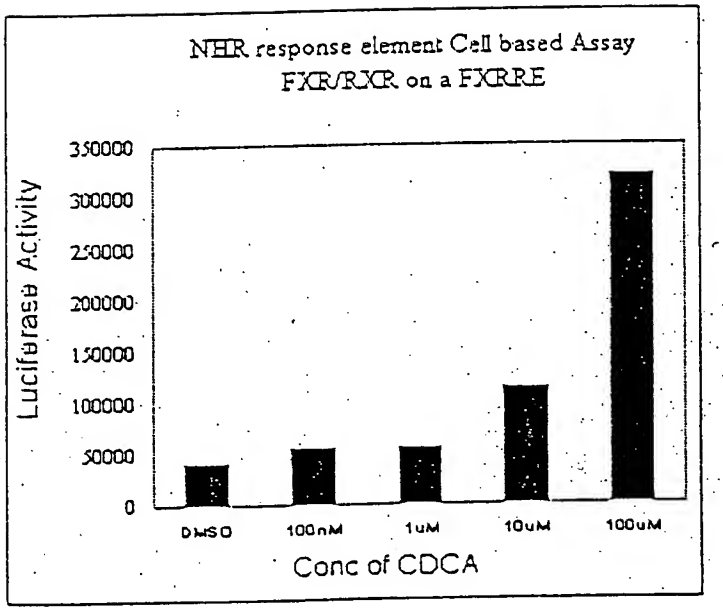
FIG. 28



Region I: Methyl acrylate or allylic methyl ether necessary for optimum activity. In some instances, when other areas were optimized, olefin can be removed while retaining some potency.
Region II: Amide or urea essential for maximum activity. Alkyl or cycloalkyl amide or urea affords most potent compounds.
Region III: Must have para-position functionalized for activity. Steric bulk and length seem to be the most important factors whcih govern potency. This region is tolerant of many different structural motifs.

Summary of structural requirements for potent FXR activation.

FIG. 29



FXR efficacy on a 384 well plate.

FIG. 30